Remarks

Claims 1-29 and 34-36 and 40-42 have been canceled without prejudice. Claims 30-33, 37-39, and 43-48 are pending. Applicants respectfully acknowledge the allowability of claims 31, 37, and 44- 47. Applicants have amended claims 32, 33, 38, and 43 as shown above and described below. Applicants have also amended the specification to incorporate disclosure provided in the original claims. Also, new claims 49-51 have been added. Support for new claim 49 can be found at least in original claim 6. New claims 50 and 51 are identical to claims 38 and 39 except that they depend from claim 48. Applicants believe that the amendments herein do not constitute new matter nor raise new issues.

Summary of Interview

Applicant would like to thank Examiners Ewoldt and Chan for their helpful comments during the interview of November 7, 2005. Regarding the written description rejection of claim 48, the primary Examiner indicated his position focused the alleged lack of written description of the construction of immunotoxin fusion protein comprising a specific anti-CD3 antibody moiety (UCHT1) and a generic disclosure of a diphtheria toxin moiety. Applicant acknowledged the Examiner's position, and indicated that they would provide evidence of support in the specification to satisfy the Examiner's rejection. The primary Examiner indicated that he would consider any support when presented to him in the present amendment.

Regarding the written description rejection of claim 30, Applicants then presented evidence in support of the claimed range that was rejected by the Examiner. The Examiners maintained that the support presented during the interview was insufficient.

35 U.S.C. § 112, first paragraph

Claims 30, 32, 33, 38, 39, 43, and 48 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide written description to reasonably convey to one of skill in the art to make or use the invention.

In particular, the Examiner has rejected claims 32 and 33 for the recitation of "optional linker." The Examiner has rejected claim 48 for the recitation of "truncated toxin moiety not

recognized by inhibitory anti-diphtheria toxin antibodies." The Examiner has rejected claims 38 and 43 for the recitation of "inhibiting rejection of transplanted tissue or organs." Lastly, the Examiner has rejected claim 30 for the recitation "152-145 carboxy terminal amino acid residues are truncated from the native diphtheria toxin moiety."

Regarding the rejection of claims 32 and 33 under 35 U.S.C. 112, first paragraph, the Examiner states that the "cited disclosures do not teach optional linkers." Applicants have amended claim 32 to remove the phrase "optionally via a linker." Support for the linking of DT390 "via its carboxy terminus to the single-chain variable region of the anti-CD3 antibody" can be found at least in Figures 11, 13, and 15. Applicants have also amended claim 33 to remove the term "optionally." Thus, the amended claim now recites "via a linker." Support for the linking of variable light and heavy domains via a linker o f claim 33 can be found throughout the application and at least on page 40, lines 26-30, page 48, lines 12-14, page 55, lies 13-17, and Figures 4, 11, and 12. In light of these amendments, applicants believe this rejection to be moot and respectfully request its withdrawal.

Regarding the rejection of claim 48 under 35 U.S.C. 112, first paragraph, the Examiner alleges that there is a lack of written description support for a fusion immunotoxin comprising UCHT1 and a generic diphtheria toxin moiety. Applicants note that original claims 4-7 all describe immunotoxins comprising UCHT1 and, generically, a mutant diphtheria toxin moiety. For example, original claim 4 recites "the immunotoxin of claim 1, wherein the antibody comprises the UCHT1 V_LV_H region. Because original claim 4 is dependent on original claim 1, the limitations of claim 1 must be read into claim 4. Original claim 1 recites "an immunotoxin, comprising a mutant diphtheria toxin moiety linked to a single chain variable region antibody which routes by the anti-CD3 pathway, or derivatives thereof." Thus, claim 4 importing the limitations of claim 1 recites "an immunotoxin, comprising a mutant diphtheria toxin moiety linked to a single chain variable region antibody which routes by the anti-CD3 pathway, or derivatives thereof, wherein the antibody comprises the UCHT1 V_LV_H region." Similarly, original claim 5 recites "the immunotoxin of claim 4, wherein the antibody comprises human CH2 and CH3 regions." By importing the limitations of the claims from which claim 5 is

dependent, claim 5 recites "an immunotoxin, comprising a mutant diphtheria toxin moiety linked to a single chain variable region antibody which routes by the anti-CD3 pathway, or derivatives thereof, wherein the antibody comprises the UCHT1 V_LV_H region, wherein the antibody comprises human CH2 and CH3 regions." Additionally, because original claim 6 recites "the immunotoxin of claim 5, wherein the antibody is divalent scUCHT1," and depends from claims 1, 4, and 5, it includes all the limitations of those claims and therefore recites "an immunotoxin, comprising a mutant diphtheria toxin moiety linked to a single chain variable region antibody which routes by the anti-CD3 pathway, or derivatives thereof, wherein the antibody comprises the UCHT1 V_LV_H region, wherein the antibody comprises human CH2 and CH3 regions, and wherein the antibody is divalent scUCHT1. Thus new claim 49 is also supported.

Applicants respectfully remind the Examiner that the original claims are considered "part of the disclosure and therefore, if an application as originally filed contains a claim disclosing material not disclosed in the remainder of the specification the applicant may amend the specification to include the claimed subject matter." MPEP 2163.06. Thus, Applicants have amended the specification to include the disclosure of originally filed claims reciting an immunotoxin comprising UCHT1 and a generic diphtheria toxin moiety. Thus, not only are claims 48 and 49 supported in the application as filed, the specification has been amended to provide explicit antecedent basis for the language of claims 48 and 49. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Regarding the rejection of claims 38 and 43, as well as support for new claim 50, the Examiner contends that the claims "encompass the inhibition of rejection in *any* species, while only rhesus monkey is disclosed, and *any* type of tissue or organ, while only skin and kidney are disclosed." Applicants have amended claims 38 and 43 to recite "mismatched kidney transplants" (applicants note that the induction of tolerance would prevent the mounting of an immune response, thus the factors that contribute to the rejection of a grafted kidney would be suppressed). Support for these amendments can be found at least on page 40, lines 5-7, where the use of immunotoxins as an adjunct to induce tolerance to mismatched kidney transplants is discussed. The Examiner further alleges that the disclosure is not adequate for the use of the

claimed immunotoxin in the methods of inhibiting kidney transplantation rejection. Applicants respectfully point out that the example on page 40, lines 5-7 provides literal support for methods of inhibiting rejection of mismatched kidney transplants. If the Examiner is focusing on the use of the immunotoxin FN18-CRM9 to induce tolerance to mismatched kidney transplants, Applicants point out, as indicated on page 27, lines 32-36 and page 39, line 35 through page 40 line 7 that FN18-CRM9 is the rhesus monkey analog of UCHT1-CRM9. FN18-CRM9 was used to show efficacy in reducing T cell count in the closest model available to humans. Applicants respectfully remind the Examiner that there is no per se rule requiring human data. Moreover, the description of using FN18-CRM9 to inhibit mismatched kidney transplant rejection is provided in the context description of methods for treating medical problems using UCHT1-CRM9. Thus, the use of the immunotoxin in humans to inhibit the rejection of kidney transplants was clearly contemplated and in Applicants' possession.

Applicants respectfully remind the Examiner that the method of claims 38, 43, and 50 work by the same mechanics as the methods of claims 39, 44, and 51. That is, as shown throughout Example 7 of the specification and in particular on page 31, lines 17-19 and page 32, lines 19-26, transplant rejection is inhibited by inducing tolerance to the transplanted tissue by depleting the T cell population. In fact, the disclosed method mechanistically would work the same way whether used for skin-allograft rejection, mismatched kidney rejection, or any other transplant rejection. Therefore, there is no difference would necessitate further reduction to practice in additional tissues once the method was shown to work for one tissue. Applicants have shown the method works and explicitly described the use of the method to inhibit mismatched kidney rejection.

Furthermore, with respect to claim 43, because CRM9 is a full-length toxin moiety and, as shown on page 40, lines 9-32, the efficacy of a full-length toxin would be inhibited by pre-existing anti-diphtheria toxin antibodies in humans immunized against diphtheria, a truncation mutant of the full-length diphtheria toxin moiety must be used in humans. As discussed throughout the application DT390 is a truncation mutant specifically designed to avoid the anti-

diphtheria antibody response. Therefore, the use of UCHT1-DT390 to inhibit transplant rejection was in Applicants' possession.

Applicants respectfully point out that the mere use of UCHT1 as the anti-CD3 antibody moiety restricts the claims to a human subject as the antibody is known to be a human anti-CD3 antibody and would not work in another species. One of skill in the art would also clearly know that experiments in monkeys using FN18 are representative of the use of UCHT1 in humans. Thus, the claims could not possibly encompass any species other than human. Moreover, as clearly discussed on page 40, lines 9-24, the entire purpose of truncating the diphtheria toxin moiety is to avoid pre-existing anti-diphtheria toxin antibodies present in human subjects as a result of immunizations against diphtheria. One of skill in the art reading claims 38 and 43 would clearly know that because a truncated toxin moiety and a human anti-CD3 antibody moiety were being used in the fusion immunotoxin, the only suitable subject would be a human. Therefore, the claims do not encompass any species, but are restricted to human subjects.

Applicants note that because kidneys transplants were previously considered by the examiner and the use of the UCHT1 antibody makes human subjects an inherent property of the claims, no new issues are raised by these amendments and no new search is necessary. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Regarding the Examiner's rejection of claim 30, the Examiner stated in the July 1, 2005, Office Action that "the fact that Applicant disclosed 3 of the 8 species that would fall within the claimed range does not demonstrate that Applicant envisioned the entire range, with all of the species in it."

Applicants respectfully point out that "range" as currently claimed actually refers to 8 disclosed species of diphtheria toxin truncation mutants. The claimed range is defined as diphtheria toxin mutants with truncations of 152-145 amino acid residues at the carboxy terminal end. DT390, DT383, and MSPΔ5 represent a truncation of 145, 152, and 150 carboxy terminal residues respectively. One of skill in the art would recognize that a description of a 152 carboxy terminal truncation mutant literally encompasses (i.e., discloses) a 145 amino acid truncation mutant, a 146 amino acid truncation mutant, a 147 amino acid truncation mutant, a 148 amino

acid truncation mutant, a 149 amino acid truncation mutant, a 150 amino acid truncation mutant, a 151 amino acid truncation mutant, and a 152 amino acid truncation mutant. This is because the possession of a 152 amino acid truncation mutant necessarily comprises a 1, 10, 20 , 30 , 40 , 100, 125, 145, 146, 147, 148, 149, 150, 151, and 152 amino acid truncation, as well as, any other truncation between 1 and 152 amino acids. Applicants have merely limited the number of mutants they wish to claim by limiting the claim to those truncation mutants within the exemplified range, i.e. those having 145 to 152 amino acids truncated. Applicants have provided description of three working examples within the claimed "range." Thus, 3 of the 8 possible mutants (37.5% of the mutants) within the "range" claimed are exemplified in the specification. Moreover, two of the truncations (145 and 152) represent the ends of the "range" and a third (150) is a truncation within the claimed "range." Furthermore, because the Applicants have exemplified the shortest and longest truncation mutants amongst those mutants they wish to claim, the exact sequence of the intermediate truncation mutants are known as the shortest truncation (the 145 carboxy terminal truncation mutant) would necessarily comprise the amino acids between 145 and 152. Thus, for any truncation mutant between 145 and 152, Applicants have literally encompassed every truncation mutant from 145 to 152 amino acids and have also provided the sequence for each mutant. Given the nature of the element at issue, a truncation, the skilled person would recognize from the disclosure of the longest and shortest truncation that all truncations encompassed by the longest and shortest truncation (i.e., the range "152-145") are in applicants' possession. There is no other way to interpret the teaching of both the longest and shortest truncation. For at least this reason, Applicants believe the rejection is overcome and should be withdrawn.

Although applicants range does not represent a genus, but rather a defined set of species, arguments regarding written description of a genus are not required. However, because some aspects of the present rejection suggest that the range could be viewed as a genus and rejections made along those lines, a response on that issue is provided. In the present application, Applicants have shown the ends and an intermediate of the claimed range (3 out of 8 members (37.5%)). Here, the specific intermediate species is described and exemplified as possessing the

same recited function as both the longest and shortest truncations of the recited "range." Applicants have also shown all three species behave identically and that one of skill in the art would recognize that other members of the genus of 8 would behave in the same manner. Applicants "function and unpredictability" arguments are relevant to show that Applicants have provided a representative number of species to claim the genus. MPEP2163.05 clearly states that "'a representative number of species' means that the species which are adequately described are representative of the entire genus." Thus, variation in the genus, if present, must be reflected in the species described. Nevertheless, "there may be situations where one species adequately supports a genus." *In re Rasmussen* 650 F.2d 1212, 1214 (CCPA 1981). In alleging the "first paragraph of USC 112 is not satisfied by subject matter that is not disclosed, but might be obvious," the Examiner is conceding Applicants' point that the other species of the genus are wholly predictable.

Moreover, as noted above, even a single species can be sufficiently representative to provide descriptive support for the claim of a genus. *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."). The MPEP further states that the sufficiency of a number of species to represent a claimed genus "depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." Moreover, Applicants would like to direct the Examiner's attention to Example 16 on page 59 of the "Revised Interim Written Description Guidelines Training Materials" (publicly available on the Home Page of the USPTO) and referred to herein as the "Guidelines." Example 16 of the Guidelines sets forth that when the level of skill and knowledge in the art is high and advanced, the written description requirements may be met

when a genus is contemplated, but no example taught in the specification. The claimed set of 8 molecules with disclosed sequences meets this test. In Example 16, the scenario and claims refer to the advanced level of skill and predictability in the art of antibody production. Applicants assert that the same is true for truncation mutants. In the Guidelines, written description was found, because the antigen was known, the method of making antibodies was known, and the structural features of antibodies were known. Here, the sequence of the native diphtheria toxin is known, the art of making truncations is known, and the structural and functional features desired in the mutants were known (desired features being those that would retain toxicity without generating an anti-diphtheria toxin antibody response was known and represented by the largest and smallest truncation). The present case is in fact the converse of claim 2 provided in Example 13 of the Guidelines. There, claim 2 was drawn to a variant of a known SEQ ID NO: 3. Variant was described as including substitutions, deletions, insertions and/or additions. However, no guidance was provided in the specification as to common attributes of the genus or the scope of the variations. Thus, the claim was invalid. Here, there the diphtheria toxin sequence is known and deletion mutants of the native toxin are claimed. Unlike the facts in Example 13, the present specification provides guidance not only in the way of common attributes of the 8 claimed deletion mutants (retain toxicity without generating an anti-diphtheria toxin antibody response) but also provides the exact structure of each of the deletion mutants (145-152 amino acids). The specification and claims provide the necessary guidance for distinguishing what is claimed from other mutants. Thus, if claim 30 is viewed a a genus claim, this case is a perfect example of a representative number of species satisfying the written description requirement for a genus.

In response to the Examiner's statement that "all limitations must appear in the specification," applicants remind the Examiner that it is not necessary for the applicants to provide literal written description of for the language of the claims. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1564 (Fed. Cir. 1991); Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)

(stating "the description need not be in *ipsis verbis* to be sufficient"). It is also not legally necessary to provide description of each and every position within the range to have written support sufficient to convey to one of skill in the art that applicants were in possession of the range at the time the application was filed. In the present situation, requiring additional examples to meet the possession requirement for this type of range amounts to a *de facto* requirement that every value within the range be exemplified. Such a de *facto* requirement is just as improper as a *per se* requirement would be under the proper legal standard. Clearly this range of truncations and these specific truncations are supported by the disclosed mutants. Description for this range can be found at least on page 9, lines 15-19; page 13, lines 13-24, and figures 17 and 18 wherein DT390, DT383, and DT370 are described. Support may also be found on page 39, lines 11-14 and page 48, lines 32-35 which describe the residues to which anti-DT antibodies in human serum are directed. Additionally support may be found on page 48, lines 10-1 which describes MSPΔ5 (a 150 residue truncation mutant) and on page 49, lines 3-6 which describes DT390 being a truncation mutant having only the first 390 of 525 residues (ie., a 145 residue truncation). Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application are believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,020.00 (fee for a three (3) month extension of time) and a Request for Extension of Time is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C

J. Gibson Lanier, Ph.D.
Registration No. 57,519

NEEDLE & ROSENBERG, P.C.
Suite 1000
999 Peachtree Street
Atlanta, Georgia 30309-3915
678-420-9300 (Tel)
678-420-9301 (Fax)

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J. Gibson Lanier, Ph.D. — Date 1/3/06